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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,725	11/30/2001	Wely B. Floriano	06618-607002	4307

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FISH & RICHARDSON, PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
WHALEY, PABLO S	
ART UNIT	PAPER NUMBER
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/010,725	FLORIANO ET AL.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-16,29,31 and 36-55* is/are pending in the application.

4a) Of the above claim(s) *48,49,52 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-16, 29, 31, 36-47, 50, 51, 53, and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

NON-ELECTED INVENTION

Newly submitted claims 48, 49, 52, and 55 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP § 806.05(e)). In this case the system could be used in any number of materially different processes, such as automated sequence alignment. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 48, 49, 52, and 55 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

CLAIMS UNDER EXAMINATION

Claims herein under examination are 1, 2, 4, 6, 9-14, 16, 31, 36-42, 45, 46, 47, 50, 51, 53, and 54. Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, 45, 46, 47, 48-55 are pending and claims 3, 5, 7, 8, 15, 17-30, 32-35, 43, and 44 have been cancelled. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied, as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, 45, 46, 47, 50, 51, 53, and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These rejections are necessitated by amendment.

Amended claims 1 and 31 now recite the term "best conformations." The term "best" is a relative term of degree, therefore it is unclear on what basis said conformations are evaluated in order to be considered "best conformations" (e.g. lowest energy, etc.). Clarification is requested.

Amended claims 1 and 31 now recite the functional limitation "using annealing molecular dynamics including solvation effects to further optimize a subset of the best conformations." It is unclear in what way "annealing molecular dynamics" includes solvation effects. It is noted that molecular dynamics (MD) models and solvation models are known in the art as distinct techniques for optimization. Clarification is requested. The Examiner has interpreted this limitation broadly for purposes of applying prior art.

Amended claims 1 and 31 now recite the term "optimizing the best conformations using molecular mechanics." As the specification does not define or fully and completely describe "molecular mechanics" for carrying out the intended function, it is unclear as to the metes and bounds intended by applicant for this limitation. Clarification is requested. The Examiner has interpreted this limitation broadly for purposes of applying prior art.

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 9, 11, 12, 16, 29, 31, 36, 37, 39, 40, 46, 47, 50, 51, 53, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by DeWitte et al. (*J. Am. Chem. Soc.*, 1996, Vol.118, p. 11733-11744).

Applicant's arguments, filed 12/28/2006, that Dewitte et al. do not teach (i) optimizing a selection of best configurations using molecular mechanics, (ii) or using annealing molecular dynamics including solvations techniques to further optimize a subset of the best conformations have been fully considered but are not persuasive for the reasons set forth below. This rejection is maintained, reiterated, and further applied to claims 47, 50, 51, 53, and 54 as necessitated by amendment.

Regarding argument (i): According to www.answers.com: "molecular mechanics" is an empirical method of calculating the dynamics of molecules, in which bonds between atoms are

represented by springs obeying Hooke's law, and additional terms representing bond angle bending, torsional interactions, and van der Waals-type interactions are included. Also known as the force-field method. The specification discloses several such programs that utilize a force-field method (e.g. CHARM, AMBER) [0007]. Dewitte et al. indeed teach the use of CHARMM for minimization (i.e. optimization) of interaction energies of designed ligands [Fig. 5] and [p. 11737, Col. 2, ¶ 1], as in new claims 50 and 51. Therefore, the Examiner maintains that Dewitte et al. indeed teach optimizing a selection of best configurations using molecular mechanics, as in amended claim 1.

Regarding argument (ii): The specification does not provide a limiting definition for the term "annealing molecular dynamics", therefore the Examiner has broadly interpreted this limitation for purposes of applying prior art. Dewitte et al. teach a course-grained docking algorithm (i.e. Monte Carlo growth algorithm) to identify a plurality of binding conformations with low energy configurations [p.11735, Col. 1, ¶ 2] that includes solvation effects for scoring (i.e. optimization) [p.11735, Col. 2, ¶ 4], as in new claims 53 and 54. Furthermore, said algorithm includes temperature control variables [p.11736, Col. 1, ¶ 4] wherein temperature is optimized to generate the largest number of low energy structures [p.11736, Col. 1, ¶ 7 and Col. 2, ¶ 1]. Therefore, the Examiner has broadly interpreted this as an implicit teaching for "using annealing molecular dynamics including solvation effects" for further optimization of designed ligands, as in amended claim 1. Furthermore, Dewitte et al. teach minimization of a "preferred set of conformations" from the subset of best design ligands and best CHARMM ligands [Fig. 5], as in amended claim 1. Furthermore, the SMOG program outputs selected conformations [Table 3], as in amended claim 1, and provides for clustering of optimized conformations [Table 5], as in amended claim 4. This rejection is therefore reiterated.

DeWitte et al. disclose the use of SmoG (Small Molecule Growth), a model for ligand-protein interactions and a scoring directly related to free energy through knowledge-based potential. A large number of structures are examined by an efficient metropolis Monte Carlo molecular growth (i.e. molecular dynamic) algorithm that generates molecules through the adjoining of functional groups directly into the binding region (Abstract), as in instant Claims 1, 4, 29, and 31. The Monte Carlo growth algorithm samples the configuration space and the molecular space under the bias of knowledge-based energy, using a coarse-grained ligand design search space (p. 11735, Col. 1, Lines 17-23). For purposes of examination, the aforementioned molecular growth algorithm has been interpreted as being within the scope of "mapping of the empty volume" (as in instant Claim 36), as it "generates molecules through the adjoining of functional groups directly into the binding region" (Abstract).

Coarse-graining has included entropic effects of solvation, and the reference state has provided the effects of solvation energy and configurational entropy (p. 11735, Col. 2, paragraph 4). As with all Monte Carlo algorithms, the algorithmic temperature defines how the algorithm responds to steps which increase the parameter being minimized (i.e. optimized) (Fig. 1, p. 11736). Thus this is a temperature dependent (i.e. annealing) molecular dynamic algorithm, as in instant Claim 1.

The model is used to score candidate structures by an evaluation (i.e. ranking) of the total binding free energy (p. 11735, Col. 2, paragraph 3). as in instant claims 1, 29, 31, and 36.

DeWitte et al. disclose preliminary selection of the lowest allowed rotamer. Atom pairs within 70% of the sum of the Van der Waals' radii are subject to energetic evaluation. The rotamer with the lowest energy is considered as a candidate for acceptance into the new molecule, as in instant Claim 8. This acceptance is determined by Monte Carlo criterion, which compares the new energy per atom with that before this growth step (p. 11736, Col. 1,

paragraph 4). Results were corroborated with the enthalpic comparison performed using a well-accepted empirical force field (p. 11743, Col. 2, paragraph 2), as in instant Claim 9.

Selection of the optimal running temperature (i.e. optimization) was made by observing the distribution of energies and computation time at different temperatures (Fig. 1 and Fig. 2), as in Claims 1 and 31. The optimal algorithmic temperature generates the largest number of low energy structures per unit time.

DeWitte et al. disclose the calculation of correlations between the design energy and an estimation of binding energy using CHARMM, an empirical force field (i.e. full atom force field)(p. 11737, col. 1, paragraph 5), as in instant claims 9 and 37.

DeWitte et al. disclose a scoring method called GROW that includes empirical interaction energy and internal energy as well as surface area terms to approximate solvent effects (p. 11742, col. 2, paragraph 1), as in instant claims 11 and 39.

DeWitte et al. disclose EQUATION 1 (below) for calculating the binding energy for each ligand in the set of ligands that includes taking the difference in the ligand energy in the protein ($-T\Delta S_{complex\ formation}$) and in solution ($-T\Delta S_{solvation/desolvation}$), as in instant claims 12 and 40.

This method is able to discriminate between potential ligands that have a high probability of binding and those that do not (i.e. ranking of candidate binding energies), and is also capable of generating the favorable candidates quickly (i.e. via selection of optimal candidate binding energies) (p. 11744, Col. 1, paragraph 4). SmoG provides several advantages including simple efficient (each molecule taking just seconds on a computer), generating and evaluating whole molecules rather than separate fragments, and documented correlation between the scoring method and free energies of binding (p. 11744, Col. 2, paragraph 3), as in instant Claims 1 and 31.

DeWitte et al. disclose an example of de novo design using the protein using SmoG and CD4, an immunoglobin-family transmembrane coreceptor expressed in the helper T-cells (p. 11740, col. 1, paragraph 1), as in instant claim 16.

DeWitte et al. further disclose that by the careful choice of a contact-based interaction model, their interaction potential reflects the trends in binding free energy without free parameters, thus eliminating the need for a series of known related ligands in the hunt for a lead compound, thus enabling the use of unknown ligands (i.e. binding regions) as in instant Claim 3.

SmoG can be operated in automated, directed, or assisted modes. Automatic generation, for example, requires only the input of the protein structure (e.g. binding pocket on the CD4 protein discussed on p. 11740, Example of de novo design-CD4) and a coordinate used to specify the vicinity of the binding site, from which it proceeds to generate ligands within 5 angstroms of the specified coordinate (p. 11737, Lines 18-22), as in instant Claim 2 and 16. Computations were carried out on a 100MHz Pentium computer running Linux (p. 11737, Line 14), which clearly discloses a computer program product as in Claims 31 and 36.

Therefore, DeWitte et al. anticipates instant claims 1, 2, 4, 9, 11, 12, 16, 29, 31, 36, 37, 39, 40, 46. Claims 47, 50, 51, 53, and 54 are also rejected for reasons set forth above.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Claims 1, 2, 4, 9, 11, 12, 16, 29, 31, 36-40, and 43-45 are rejected under the first paragraph of 35 USC § 103(a) as being unpatentable over Zou et al. (1999), in further view of DeWitte et al. (DeWitte R., Shakhnovich E., *J. Am. Chem. Soc.*, 1996, 118: 11733-11744).

Applicant's response, filed 12/28/2006, indicated uncertainty as to whether the cited "Zou et al." reference used in the instant rejection was the same Zou et al. used in the previous rejection or a different Zou et al. The Examiner would like to clarify that correct publication for the Zou et al. reference is Zou et al (J. Am. Chem. Soc., 1999, Vol. 121, p.8033-8043), as pointed out by applicant in the response [p.25]. Applicant's arguments that Zou et al. do not teach or suggest the use of annealing molecular dynamics are not persuasive for the reasons set forth below. This rejection is maintained.

In response, applicant's priority document 60/213,658, filed 6/23/2000, teaches that annealing dynamics can be practiced using a generalized Born model [p.8]. The method of Zou et al. teaches a generalized Born surface area model (GB/SA) to compute ligand binding energies wherein the parameters are approximated by a linear dependence on the solvent-accessible surface area and dielectric properties around the binding site as directed to the unoccupied embedded space (page 8034, 11. Method §, column 2, to page 8035, column 1, line 26). Thus, Zou et al. provide an implicit teaching for annealing molecular dynamics. Furthermore, the Examiner maintains that Dewitte et al. teach a course-grained docking algorithm (i.e. Monte Carlo growth algorithm) to identify a plurality of binding conformations with low energy configurations [p.11735, Col. 1, ¶ 2] that includes solvation effects for scoring (i.e. optimization) [p.11735, Col. 2, ¶ 4]. Furthermore, said algorithm includes temperature control variables [p.11736, Col. 1, ¶ 4] wherein temperature is optimized to generate the largest number of low energy structures [p.11736, Col. 1, ¶ 7 and Col. 2, ¶ 1]. Therefore, in response to the

arguments that Zou et al. do not teach the instantly claimed method, and that Dewitte et al. do not "solve" the argued deficiencies of Zou et al., it is noted that the examiner maintains that Zou et al. do, in fact, teach the claimed invention for the reasons set forth above and in the previous office action. As the examiner maintains that Zou et al. teach the limitations of instant claims 1, 2, 4, 9, 11, 12, 16, 29, 31, 36-40, and 43-45, as set forth in the previous office action and maintained above, he also maintains that Zou et al. combined with Dewitte et al. make obvious claims 1, 2, 4, 9, 11, 12, 16, 29, 31, 36-40, and 43-45 for the reasons and motivation previously set forth.

CONCLUSION

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pablo S. Whaley

Patent Examiner
Art Unit 1631
Office: 571-272-4425

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER